Original Article

Juvenile Idiopathic Arthritis: Etiopathogenesis, Therapy And Outcomes

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Abstract

Summary

Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease in children and is classified according to the criteria of the International League of Rheumatological Associations. JIA is divided into oligoarticular, polyarticular, systemic, psoriatic, enthesitis-like, and undifferentiated arthritis, depending on the number of affected joints, the presence of extra-articular manifestations, systemic symptoms, serological changes, and genetic factors. This article provides an overview of advances in understanding JIA pathogenesis, etiology, histopathology, immunological changes consistent with disease activity, and treatment options. JIA is discussed in the context of treatment, including traditional non-biological and modern biologic antirheumatic drugs. However, a significant number of patients remain refractory to treatment, although the advent of advanced therapeutic methods has improved clinical outcomes, which necessitates further understanding of the progression and remission of the disease in order to select adequate therapy.

Keywords: juvenile idiopathic arthritis, pathogenesis of juvenile idiopathic arthritis, etiology of juvenile idiopathic arthritis, antirheumatic drug therapy

Definition and classification

Juvenile idiopathic arthritis (JIA) - all forms of chronic arthritis in children that affect the joints, extra-articular structures, including the eyes, skin and internal organs, leading to disability and death. It is defined as the presence of arthritis of unknown etiology that begins before the age of 16 and persists for at least 6 weeks [1].

The main characteristics of arthritis are visceral involvement, genetic predisposition, laboratory markers of each subtype and adult equivalent. Oligoarticular JIA is characterized by inflammation of up to four joints, which proceeds as asymmetric arthritis with a predominant lesion of the joints of the lower extremities of the knee and ankle, with a high frequency of antinuclear antibodies (ANA) positivity and a high risk of chronic uveitis [2].

Polyarticular (pJIA) affects five or more large/small joints and is characterized by involvement of the metacarpophalangeal joints and wrists [3]. RF-positive and RF-negative variants have characteristic clinical features. In RF-negative pJIA, inflammation may be asymmetrical, but in RF-positive pJIA, symmetrical involvement of the large and small joints of the

hands and feet is most common. Enthesitis-like arthritis (EPA) resembles oligoarthritis, affecting the joints of the lower extremities in association with enthesitis. Ravelli et al., classified EPA as a spondyloarthropathy [2] due to associations with the lower extremities and sacroiliac joints, enthesitis, uveitis, and association with HLAB27.

Psoriatic JIA (psJIA) is described as a heterogeneous disease that occurs more often in children under 6 years of age with a predominance of girls, positive antinuclear antibodies and a predisposition to chronic uveitis, dactylitis with arthritis of the wrists and small joints of the hands and feet, psoriatic rash and/or ulceration nails [1, 3]. In older children, the disease is associated with HLA-B27 positivity, enthesitis, and axial disease with a male predisposition [4].

Systemic JIA (sJIA), unlike other subtypes, manifests itself not only in widespread articular arthritis, but also in severe symptoms of systemic inflammation [5, 6, 7]. 10% of patients with sJIA have systemic symptoms with associated macrophage activation syndrome (MAS), a potentially life-threatening condition with histopathological features that include accumulation of terminally differentiated macrophages with high hemophagocytic activity, lung involvement in the form of pulmonary hypertension, interstitial lesions, and alveolar proteinosis [8, 9].

There is also a significant unclassified cohort of patients with JIA onset before the age of 6 years, predominantly female, with specific features including symmetrical arthritis, iridocyclitis, ANA, and HLA-DR8 positivity. In 2019, the Consensus of the International Organization of Pediatric Rheumatology (PRINTO) revised the classification criteria for ILAR and proposed to identify this set of features as early ANA-positive JIA [10, 11]. Based on these preliminary criteria, other JIA disorders identified include sJIA, RF-positive JIA, and JIA associated with enthesitis/spondylitis. Arthritis lasting more than 6 weeks that does not meet the criteria is classified as “other JIA”, and that meets more than one criterion as “unclassified JIA”. PRINTO Consensus distinguishes JIA not as a single disease, but as a group of different disorders, the diagnosis of which does not require a joint count or the presence of arthritis. The onset of the disease was changed to age up to 18 years [11].

Pathological and histological changes in JIA

Inflammation of the joints with tissue destruction is the main symptom of JIA. The synovial membrane of the joint thickens in response to the uncontrolled proliferation of synoviocytes and immunocompetent cells, including T cells, B cells, natural killer cells, neutrophils, macrophages, dendritic cells, and plasma cells, which infiltrate the submucosal layer of the synovial membrane [12].Hyperplasia and hypertrophy of the synovial membrane cause intraarticular hypoxia, enhancing the production of proangiogenic mediators and initiating pathological angiogenesis [13]. Elevated concentrations of vascular endothelial growth factor (VEGF), a potent endothelial cell (EC) mitogen, its soluble receptors-1 and -2 (sVEGF-R1, sVEGF-R2), and osteopontin, a chemotactic factor that activates mononuclear cells, correlate with synovial angiogenesis, assessed Doppler ultrasound in patients with JIA. JIA activates angiopoietin-1 (Ang-1), another pro-angiogenic EC mitogen that plays a role in stabilizing newly formed vessels. As a result of the formation of new blood vessels in the synovium, the blood supply and migration of pro-inflammatory cells to the joint increases, thus forming an abnormal synovial membrane, known as "pannus" [13].

Granulocytes, macrophages, plasma cells and lymphocytes accumulate in the subintim of the joint and produce pro-inflammatory mediators, including tumor necrosis factor-α (TNFα) and interleukin IL1β, increasing the production of catabolic proteases by pannus synoviocytes, including matrix metalloproteinases (MMPs), especially MMP1 and MMP3, agrekinases and cathepsins, which destroy the extracellular matrix of articular cartilage tissue, causing loss of function, biomechanical strength, and the ability to smoothly articulate the joint [2, 14]. Pro-inflammatory cytokine-mediated activation of osteoclasts expressing the nuclear factor kappa B receptor activator (RANK) leads to bone erosion. Damage to cartilage and bones in the late stages of JIA causes ankylosis and loss of mobility in the affected joints. JIA is a disease of the developing organism, and in this regard, patients with JIA are likely to suffer from impaired skeletal growth [15].

Etiology

Environmental factors have been proposed as risk factors, including infectious agents, vaccinations, antibiotics, vitamin D deficiency, stress, and trauma. Infectious viruses (Epstein-Barr virus, parvovirus B, rubivirus, hepatitis B virus) and bacteria (Salmonella spp., Shigella spp., Campylobacter spp., S. pyogenes, B. henselae, M. pneumoniae, Chlamydophila pneumonia) have been reported as causal factors provoking JIA [16, 17)]. Gastrointestinal infection, leading to loss of gut microbiome diversity and disruption of tryptophan metabolism, increases the risk of EPA [18]. According to Carlens C.et.al. (2009) maternal smoking during pregnancy increases the likelihood of an immune imbalance during fetal development, leading to the onset and progression of childhood arthritis, while breastfeeding may reduce the risk of developing JIA [19, 20].

In recent years, there have been a number of reports of genetic associations with JIA [21, 22, 23]. Genetic linkage is subtype dependent and can be divided into two groups: HLA genes and non-HLA genes. Meta-analysis of genetic predisposition to JIA subtypes showed an association with HLA class II molecules (A2, DRB1, DPB1) predominantly for non-systemic subtypes, while no association with HLA genes was found for sJIA [19]. Oligoarticular JIA is associated with A2, DRB1*11, DRB1*08, DPB1*02, DRB1*13, DRB1*15*01, and DRB1*01, while DPB1:03 and DRB1 are the most commonly associated genes for RF polyarthritis :08, and for RF+ JIA, DRB1*04 and DRB1*01 [21]. Interestingly, HLA-A, HLA-B, and HLA-DR were observed in women with oligoarthritis, but not in men, which may indicate the heterogeneity of the disease [2]. The main gene associated with EPA and psoriatic JIA is HLA-B27, and other genes that predispose to the development of EPA are DRB1*01, DQA1*01 and DQB1*05 [17,18]. The genetic predisposition of genes not associated with HLA plays a key role in the occurrence of an inflammatory response leading to tissue damage. Genes encoding cytokines TNF, IL2, IL10, IL6, macrophage migration inhibitory factor (FIMM), protein tyrosine phosphatase (PTPN22), signal transducer and transcription activator-4 (STAT4), solute transporter family-11 (proton-bound divalent ion metal transporters), member-1 (SLC11A1), natural resistance-associated macrophage protein-1 (NRAMP1), and WNT1-induced signaling protein-3 (WISP3) are associated with JIA [2, 23, 24].

Polymorphisms in genes encoding resident endoplasmic reticulum aminopeptidases (ERAP1 and ERAP2) predispose to EPA, and genes encoding IL1, IL6, IL10, and FIMM increase the risk of sJIA, which itself is considered a genetically distinct subtype of JIA [16].

Pathogenesis and immunological changes in JIA

JIA subtypes represent a heterogeneous group of diseases with multifactorial and diverse pathogenesis. The initiation of the pathophysiological cascade of JIA includes abnormal activation of T cells, B cells, natural killer (NK), dendritic cells (DC), macrophages, and neutrophils, as well as the production of pro-inflammatory mediators that cause joint destruction and systemic complications.

Oligoarticular and pJIA are characterized by autoreactive antigen-specific T cells and high autoantibody titers and tend to show a strong association with class II MHC alleles.

Differentiation of native T cells into T cells leads to the production of the pro-inflammatory cytokine IL17, which can induce the production of IL6, MMP1 and 3, IL8 (neutrophil chemoattractant) by synoviocytes, which leads to subsequent joint destruction [16, 25].

The association with HLA class II and the presence of ANA suggests that the pathogenesis of oligoarticular JIA is dominated by an adaptive immune response. However, recently, activated neutrophils with altered phenotype and dysfunction, as well as impaired synovial monocytes and macrophages with a reduced ability to phagocytosis, have been identified in the synovial fluid of patients with oligoarticular JIA [26, 27]. In combination with a high level of monocytic cytokines, this emphasizes the importance of the innate immune system in the pathogenesis of oligoarticular JIA [28, 29].

The pathogenesis of EPA is mediated by the HLA-B27-mediated presentation of the arthritogenic peptide following T-cell activation and secretion of IL23 and IL17. Inflammation of the intestinal wall, usually accompanied by EPA, is driven by γδT cells, type 3 innate lymphoid cells or Th17 cells, and the production of IL17 and IL23 [18]. Enthesitis is triggered by repeated biomechanical stress stimulation, leading to microtrauma and release of fibronectin, hyaluronic acid, and other molecular components from damaged connective tissue, which can directly activate synovial macrophages, stromal cells, and IL23 production to establish a positive feedback loop. In contrast to the non-systemic subtypes known as autoimmune diseases, sJIA is considered to be an autoinflammatory disease with variable pathogenesis [16]. In sJIA, uncontrolled activation of the innate immune system leads to the activation of monocytes/macrophages, neutrophils, and immature (CD34+CD33+) myelomonocyte precursors, an increase in the production of proinflammatory cytokines IL1β, IL6, IL18, and phagocytospecific S100 proteins [16, 27, 28, 29]. MAS (Macrophage Activation Syndrome) is a complex sJIA in which certain triggers (bacterial or viral infections, drugs) cause an uncontrolled expansion of cytotoxic CD8+ T cells that produce pro-inflammatory cytokines and contribute to the induction and activation of hemophagocytic macrophages that infiltrate the bone marrow and many organs, in particular the liver and spleen [6, 9].

Cytokines and antibody production in JIA

In the plasma and synovial fluid of patients with JIA, there is a significant predominance of the pro-inflammatory cytokine spectrum. JIA patients show high levels of TNFα, MIF FIMM, macrophage inflammatory protein (CCL3), macrophage

chemokine (CCL22), IFNγ-induced monokine (CXCL9), monocytic chemoattractant protein-1 (CCL2), and IFNγ-induced protein-10 (CXCL10) .) in blood and synovial fluid [30].

Elevated levels of IL33 are observed in patients with RF+ polyarticular JIA compared to oligo- and RF+ polyarticular JIA and correlate with disease activity, suggesting that it is a potential candidate for pJIA disease activity biomarkers [31)]. Serum or synovial fluid concentrations of FIMM MIF, IL10, and IL17 are predictive of oligoarticular JIA (less than 60% accuracy). FIIM, IL17 and IL23 are also elevated in EPA [19].

IL18 is a predictor of sJIA (with 93% accuracy) and plays a key role in the pathogenesis of MAS, with elevated levels reported to be a predictor of SAM complications in patients with sJIA [32].

Adenosine deaminase-2 (ADA2), released by monocytes and macrophages after stimulation with IL18 and IFNγ, is considered a new MAS biomarker that strongly correlates with ferritin, IL18, and CXCL9 [33].

Thus, a clinically inactive disease in the absence of drug treatment in some patients may represent a compensation of autoimmune activity by anti-inflammatory cytokines [16].

ANA, RF, anticyclic citrullinated peptide (anti-CCP), and antibodies against mutated citrullinated vimentin (anti-MCV) have been described in the pathogenesis of non-systemic JIA [34]. RF is an antibody specific for the Fc fragment of IgG; it was first described as a key serological marker in adults with rheumatoid arthritis [5].

ANA is considered characteristic of oligoarticular, polyarticular, psoriatic subtypes of JIA and is associated with an increased risk of uveitis in patients with JIA [35].

Anti-CCP and anti-MCV commonly characterize RF-positive pJIA and may predict more severe and erosive disease progression requiring earlier and more intensive therapy [33]. Patients with double positive results for anti-CCP and RF have higher levels of TNFα, IL1β, IL6 and IL17 [34].

Diagnosis of the disease and prediction of complications

To determine the subtype of JIA, clinical symptoms, family history, laboratory markers and instrumental studies (ultrasound and magnetic resonance imaging) are used. Physical examination findings are of paramount importance and include signs of arthritis (pain, tenderness, stiffness, and swelling of the synovial joints) and extra-articular manifestations (such as rash, lymphadenopathy, dactylitis, nail changes).

Laboratory tests for HLA-B27, RF, or anti-CCP antibodies determine JIA subtype and risk for bone erosion and joint damage. Myeloid-like protein (MPP)8, MPD14, and IL18 can be used as biomarkers for active sJIA, while HLA-B27 is a predictor of EPA [34]. ANA is associated with an increased risk of chronic nongranulomatous uveitis, which is the most common extra-articular manifestation of JIA and is usually asymptomatic but has an increased risk of visual impairment [35].

According to the authors, high levels of pro-inflammatory calcium-binding proteins S100 are observed in patients with sJIA compared with other autoinflammatory syndromes. However, other studies have shown that high baseline concentrations of S100A12 are associated with higher disease activity and response to methotrexate (MTX) and anti-TNF therapy in patients with JIA, including pJIA, EPA, oligoarticular and psoriatic arthritis [35, 36].

A history of gastrointestinal or urinary infections, intestinal inflammation confirmed by elevated levels of fecal calprotectin, sacroiliitis with inflammatory changes in the spine, and enthesitis detected by MRI support the diagnosis of EPA [19].

For a diagnosis of sJIA according to the ILAR criteria, the presence of arthritis and fever within the past 2 weeks, and one of the following criteria: rash, generalized lymphadenopathy, liver or spleen enlargement, or serositis [37].

Common laboratory abnormalities indicative of systemic inflammation include elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocyte count, platelet count, ferritin, transaminases, aldolase, and d-dimers, which help determine disease activity [38].

Laboratory analysis of patients with active sJIA may reveal granulocytosis, thrombocytosis, anemia, increased acute phase reagents (increased erythrocyte sedimentation rate and C-reactive protein), which are typical signs, but not as essential for diagnosis compared with such a life-threatening complication as MAS, which includes pancytopenia, increased levels of ferritin, liver enzymes (aspartate and alanine transaminase), triglycerides, d-dimer, and hypofibrinogenemia [7].

Clinical features of MAS include high non-remitting fever, generalized lymphadenopathy, hepatosplenomegaly, central nervous system dysfunction, and hemorrhagic manifestations.

JIA treatment

Once the diagnosis is established, treatment begins with non-steroidal anti-inflammatory drugs (NSAIDs), then DMARDs (DMARDs) and/or intra-articular corticosteroid injections, and genetically engineered biological drugs (GEBDs). By blocking the production of prostaglandins by inhibiting cyclooxygenase-1 and cyclooxygenase-2, NSAIDs have both analgesic and anti-inflammatory effects [39].

Intra-articular corticosteroid injections are effective for synovitis and may be first-line treatment for oligoarthritis alone or in addition to DMARDs. Systemic administration of high doses of corticosteroids provides a good short-term effect, especially in patients with sJIA, but does not affect the long-term outcome of the disease. Moreover, its long-term administration is associated with serious side effects, including osteoporosis, growth suppression, immunosuppression, and metabolic effects. The American College of Rheumatology (ACR) recommends early administration of DMARDs, especially methotrexate (MTK), leflunomide, and/or sulfasalazine. MTK is considered a DMARD of first choice in oligo- and pJIA when the use of NSAIDs and intra-articular steroids is insufficient [40, 41].

Methotrexate is also considered effective in children with PsJIA, although axial manifestations limit the use of methotrexate, so TNF inhibitors are usually required in these cases [5]. In 30–50% of patients, when the disease progresses, the administration of biological agents is the next therapeutic step [42].

The first biologics registered for the treatment of JIA were the anti-TNFα agents, etanercept and adalimumab. Etanercept was approved for the treatment of pJIA in 1999 based on a randomized, placebo-controlled, double-blind safety and efficacy study [43].

Currently, TNFα inhibitors are recognized as the most effective drugs for the treatment of JIA with an effect on pain, stiffness, growth and quality of life and were successful first in the treatment of pJIA, then EPA, psoriatic and oligoarthritis subtypes [40, 44].

The combination of TNFα blockers with methotrexate increases the possibility of achieving JIA remission in patients with these subtypes and is an effective treatment option for uveitis-associated JIA [46]. For pJIA not responding to at least one DMARD, including TNFα inhibitors, abatacept (CTLA4-Ig) may be recommended [45, 46]. The authors showed long-term efficacy, safety, and improvement in the quality of life in 58 patients with JIA over a period of 7 years [47].

Another option, if TNFα inhibition leads to suboptimal clinical outcomes in pJIA, is the use of an IL6 receptor inhibitor, tocilizumab. Tocilizumab may also be a treatment option for uveitis caused by JIA refractory to methotrexate and TNF inhibitors [48].

Tocilizumab (anti-IL6R) was the first approved drug for the treatment of active sJIA, demonstrating safety and efficacy in two multicentre studies in patients with sJIA and pJIA [32].

Currently, anakinra (IL1Ra), rilonacept (an IL1 inhibitor), and canakinumab (anti-IL1β) have been successfully studied in clinical trials with comparable long-term efficacy, with half achieving remission [49].

MAS is usually treated with high doses of methylprednisolone and cyclosporine A (a calcineurin inhibitor), the use of the IL1 receptor antagonist anakinra (IL-1Ra) and rituximab (anti-CD20), has also been shown to be effective in other immunological disorders, including SLE [50].

Other therapies, tadekinig alfa (anti-IL-18) and emapalumab (anti-IFNγ) are currently in clinical trials, and evidence suggests safety and potential efficacy in the treatment of sJIA and MAS 51, 52].

Another new class of nother new class of biological DMARDs are the Janus-associated tyrosine kinases (JAK) inhibitors. Their mechanism of action is to block the JAK pathways, a signaling pathway for interrupting the transmission of extracellular pro-inflammatory signals to the cell nucleus. First-generation JAK (and JAK) inhibitors (namely tofacitinib and baricitinib, upadicitinib) were first studied in adults with RA and then in other immune-mediated inflammatory diseases such as ankylosing syndrome, spondylitis, SLE, inflammatory bowel disease, and psoriasis [53, 54].

Early treatment with biologics is essential to control disease activity and eliminate steroids completely or at least shorten the duration of their use. However, long-term administration of biologics due to immune suppression increases the risk of opportunistic infections and possibly even malignancies [55].

Studies have shown that with early aggressive treatment of JIA patients with GEBD, 40% of patients achieve clinical inactivity of the disease within 6 months], although some serious adverse events have been reported during treatment (such as pneumonia, septic joint, increased transaminase activity, peritonsillar abscess, recurrent herpes simplex) [56].

Progress in treatment, improvement in quality of life and outcome of JIA

Over the past decades, significant progress has been made in the treatment of JIA, clinical outcomes have improved significantly, and the majority of patients are able to control the disease and remission. However, in many patients, persistent disease activity persists. In fact, about half of patients continue to require active treatment into adulthood, while complete remission is not possible, achieved in only 20–25% of patients, and 30% suffer from some form of disability and poor quality of life [57, 58].

The introduction of biologics has reduced the mortality rate from JIA from 1–4% in the 1970s. to 0.3–1% in 2016 [59]. The improvement in clinical outcomes for physical disability is reflected in the Steinbrocker scale, a functional classification scale. Between 1976 and 1994, 15% of patients with JIA were class III (limited to little or no patient activity) and class IV (bedridden with little or no self-care) compared with 5% in 2002 [60].

In addition, the high risk of osteoporosis and, as a result, fractures in early adulthood remains higher in patients with JIA even in remission [15].

Long-term outcomes in patients with JIA depend on the subtype and activity of the disease, which may remain elevated for many years, including into adulthood. In early adulthood, about half of patients with JIA have active disease and approximately 30% have some form of disability.

Conclusion

JIA is a chronic rheumatic disease of childhood characterized by progressive joint destruction and severe systemic manifestations. Complex interactions between populations of immune cells, including lymphocytes, monocytes, macrophages, and neutrophils, trigger the pathophysiological cascade in JIA.

The heterogeneity of the pathogenesis of non-systemic and sJIA leads to the stratification of patients with JIA by subtypes with the need for different therapeutic approaches. The use of a wide range of DMARDs, such as T-cell inhibitors, anti-TNFα agents, IL1 and IL6 blockers, JAK inhibitors, has significantly improved the clinical management of JIA. This necessitates further research to deepen understanding of the complexity of the inflammatory process in JIA and develop effective treatments that improve clinical outcomes and remission of the disease

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